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Unusual Mechanistic Course of Some NHC-Mediated Transesterifications

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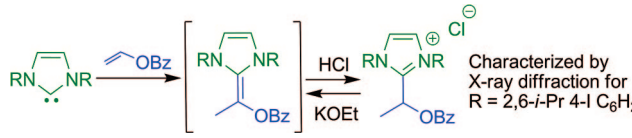
ABSTRACT



During experiments on the transesterification of vinyl benzoate with ethanol mediated by IPr and IMes, unexpected species were observed and characterized that call into question the accepted mechanism of the NHC-mediated transesterification of vinyl esters.

N-Heterocyclic carbenes (NHCs), first prepared as early as 1968[1] and isolated by Arduengo and co-workers in 1991,[2] have attracted considerable interest as both ligands for transition metals[3,4] and organocatalysts.[3,5,6] In 2002 the groups of Hedrick and Waymouth[7a] and Nolan[8a] simultaneously reported the application of NHCs to acyl transfer reactions: several structurally simple and easy-to-prepare NHCs were described to catalyze the transesterification of vinyl, methyl, and ethyl esters with primary and secondary alcohols in excellent yields. The scope of NHC-catalyzed acyl transfer has since been extended to "living" polymerizations,[7b] amidation of esters with aminoalcohols,[9] synthesis of phosphorus esters,[8d] and through the use of chiral NHCs, kinetic resolution of racemic secondary alcohols.[10,11]

Despite these successes, the mechanism of NHC-promoted transesterification remains unclear. The formation of an acylimidazolium species[12] is generally accepted by analogy with

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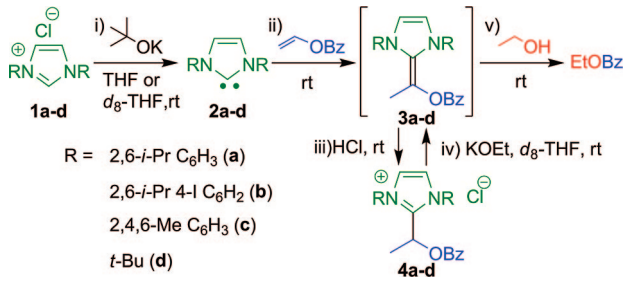
acyl-transfer reactions mediated by nitrogen nucleophiles,[8,10] while computational studies[13] indicate that the role of the NHC in catalysis is to assist proton transfer from the alcohol to the carbonyl oxygen through a hydrogen-bonded complex. The isolation and characterization of an IMes−MeOH hydrogen-bonded complex is invoked in support of the latter mechanism.[9] However, little or no direct experimental evidence has been provided in support of either hypothesis.

Here we report experimental observations on the mechanism of transesterification of vinyl esters, obtained during preliminary studies on the applicability of such reactions in the active template synthesis of interlocked architectures,[14] which run contrary to either of these mechanistic proposals.

In initial experiments (Scheme 1) the transesterification of vinyl benzoate with ethanol promoted by a stoichiometric

Scheme 1. Reaction of Carbenes **2** with Vinyl Benzoate



amount of in situ generated IPr (**2a**) proved sluggish, with little formation of ethyl benzoate observed when the reaction was quenched with ethereal HCl after 2 h. Despite the low conversion to product, ^{1}H NMR analysis of the crude reaction mixture indicated complete consumption of the vinyl ester, with the major component being an unknown imidazolium-derived compound. Intriguingly, when vinyl benzoate was added to a solution of carbene **2a** and the reaction quenched with ethereal HCl after 2 h, the major product in near quantitative yield was the same unknown species, which proved stable enough to be purified by column chromatography and was tentatively assigned as adduct **4a**. This assignment was confirmed by single crystal X-ray analysis of analogous compound **4b**, prepared in a similar manner using **1b** (Figure 1).[15]

A brief survey of previous reports on the use of vinyl esters as acyl-transfer agents in the NHC-mediated acylation of alcohols[7,8,10,11] reveals extremely variable yields: from near quantitative in the case of the IMes-mediated reaction between vinyl acetate and BnOH[7a] to between 4% and 44% in the case of NHC-mediated reactions between vinyl acetate

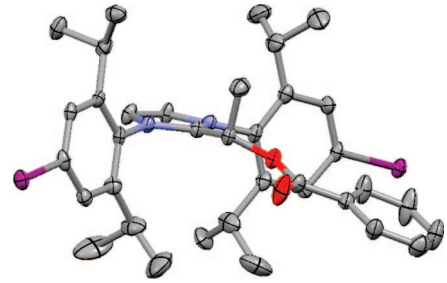


Figure 1. X-ray crystal structure of adduct **4b** with thermal ellipsoids (50% probability). Chloride counterion, solvent molecules, and hydrogen atoms are omitted for clarity.

and secondary alcohols.[10a] Intrigued by the unusual products isolated and in an effort to determine if these species play a significant role in the NHC-mediated transesterification of vinyl esters, possibly providing an explanation for the disparate yields previously reported, we investigated the reaction between IPr and vinyl benzoate by ^{1}H NMR.

When vinyl benzoate was added to IPr (**2a**) that had been generated in d_8-THF (Figure 2a), near quantitative conversion

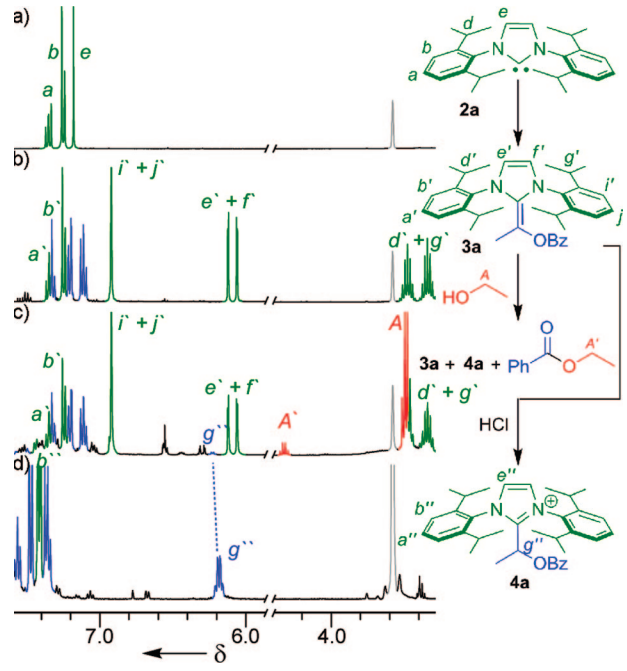


Figure 2. Partial ^{1}H NMR spectra (400 MHz, d_8-THF, 300 K) of (a) IPr (**2a**), (b) IPr + vinyl benzoate (adduct **3a**), (c) IPr + vinyl benzoate + EtOH after 3.5 h, and (d) adduct **4a**.

to a new imidazolium species (Figure 2b) was observed within 1 h. This species could not be isolated, but it proved stable enough to be characterized by ^{1}H and ^{13}C NMR as adduct **3a**, although evidence of decomposition was observed after 5 h. When EtOH (1 equiv) was added to a freshly prepared solution of adduct, slow conversion from ethanol

(11) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347–1349.
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(14) Aucagne, V.; Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Ronaldson, V. E.; Slawin, A. M. Z.; Viterisi, A.; Walker, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11950–11963.

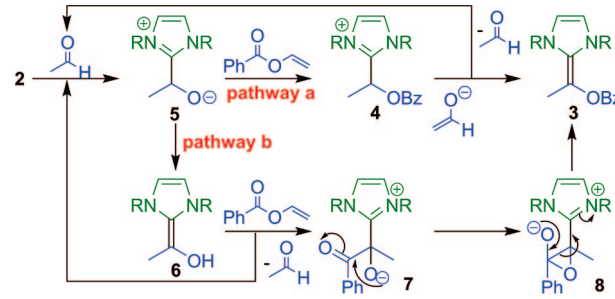
to ethyl benzoate was observed (1 h, 2%; 7 h, 10%; 24 h, 20%) accompanied by slow degradation to a complex mixture of imidazolium-containing byproducts and protonated adduct **4a** (^{1}H NMR spectrum of **4a** shown in Figure 2d). Formation of product ceased once all of adduct **3a** had been consumed. The same results were obtained when in situ generated IPr was added to a solution of vinyl benzoate and EtOH, indicating that formation of adduct **3a** takes place at a significantly higher rate than the transesterification reaction. On the other hand, when a large excess (15 equiv) of ethanol was added to preformed **3a**, full conversion to EtOBz was obtained within 50 min. When the transesterification of vinyl benzoate with EtOH was repeated in the presence of a catalytic amount of IPr (1 mol %), rapid formation of adduct **3a** was again clearly observed by NMR. As in the stoichiometric experiment, a slow transesterification process was observed (4 h, 11%). Once again, when after 8 h all of **3a** had disappeared, the reaction stopped (16% final conversion). Finally, when adduct **4a** was treated with 1 equiv of EtOK in d_8-THF, formation of **3a** took place much more quickly than the transesterification process. Taken together, these results indicate that adduct **3a** plays a central role in the IPr-promoted transesterification between vinyl benzoate and EtOH, whereas adduct **4a** is inactive to acyl transfer under the reaction conditions.

When the transesterification of vinyl benzoate in the presence of a catalytic quantity (1%) of IMes (**2c**)[7,8] was monitored by ^{1}H NMR, rapid formation of analogous adduct **3c** was observed. The lifetime of adduct **3c** was extremely short: after 5 min adduct **4c** was the only identifiable IMes-derived species remaining. However, in the presence of **2c** the transesterification process was significantly faster than with **2a**, and a conversion of 31% was obtained despite the short lifetime of **3c**.

Thus, apart from the obvious kinetic differences, the transesterification reaction between vinyl benzoate and EtOH mediated by IMes (**2c**) appears to proceed in a fashion analogous to that mediated by IPr (**2a**). However, ^{1}H NMR analysis of the reaction mediated by carbene I*t*Bu (**2d**) indicated that in this case the reaction may proceed differently. When vinyl benzoate was added to carbene **2d** (1%) in d_8-THF, no formation of adducts **3d** or **4d** was observed by ^{1}H NMR. However, addition of EtOH led to rapid transesterification (14% maximum conversion), with a small amount of adduct **4d** detected after 2 h of reaction.

Two plausible mechanisms for the formation of adduct **3** are envisaged (Scheme 2), both initiated by attack of the NHC on trace amounts of acetaldehyde.[16] The simplest mechanism then involves *O*-acylation of alkoxide **5** by vinyl benzoate followed by deprotonation of adduct **4** by the acetaldehyde enolate byproduct to give observed product **3** and regenerate acetaldehyde (pathway a). Alternatively,

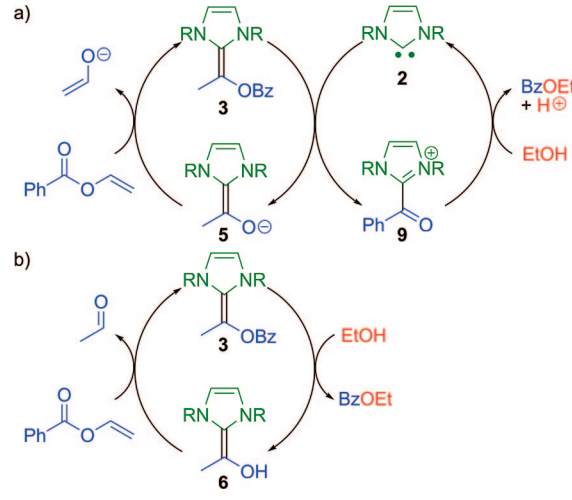
Scheme 2. Possible Mechanisms of Formation for Adduct **3**



alkoxide **5** may tautomerize to give the Breslow intermediate commonly invoked in the NHC-mediated benzoin reaction (**7**).[17] Enol **6** can then undergo *C*-acylation[18] to give intermediate **7** and regenerate acetaldehyde (pathway b). C−O migration of the benzoyl[19] group gives adduct **3** via intermediate **8**. Adduct **4** is then simply the product of protonation of adduct **3**. It should be noted that acetaldehyde is regenerated in this process, and thus only a trace amount of acetaldehyde need be present to initiate the reaction.

In light of the above results it seems clear that the IMes and IPr-mediated transesterifiction of vinyl esters are far more complicated than has previously been thought, with adducts **3** being important intermediates in the process. Two roles that can be envisaged for these species are shown: an intermediate that becomes activated by trace amounts of free carbene or an active species in its own right (Scheme 3a

Scheme 3. Possible Mechanisms of the NHC-Mediated Transesterification Reaction of Vinyl Benzoate and EtOH



and b, respectively). In cycle a, adduct **3** reverts to acyl-imidazolium species **9**, which is then attacked by EtOH to

(15) Protonated Breslow-type intermediates have been observed in NHC-mediated Baylis−Hillman reactions (Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 4673−4676; Schrader, W.; Handayani, P. P.; Burstein, C.; Glorius, F. *Chem. Commun.* **2007**, *7*, 716−718) and characterized crystallographically in the NHC-mediated addition of α-hydroxypropargylsilanes to aldehydes: Reynolds, T. E.; Stern, C. A.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 2581−2584.

(16) Trace acetaldehyde required to initiate this process may be fomed via an acyl-imidazolium species normally postulated. As suggested by one of the reviewers, this same acyl-imidazolium species may also be responsible for the acylation of **5** or **6**, and this represents a valid variation on either pathway a or pathway b.

(17) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

give the product ester and regenerate the carbene. Alternatively, cycle b is far simpler, with direct displacement of the benzoyl group from adduct **3** to give product and enol **6**, which then reacts with 1 equiv of vinyl benzoate to regenerate adduct **3** once again.

In both proposed mechanisms it seems likely that the reaction rate is significantly retarded by formation of adducts **3**: in cycle a, adducts **3** can be considered catalyst rest states, which by ^{1}H NMR appear to be the dominant form of the catalyst, whereas in cycle b, in which adducts **3** are the active species, they can be expected to be significantly less reactive than corresponding, charged, acyl-imidazolium species **9**. Thus, the acetaldehyde formed during the NHC-mediated transesterification of vinyl esters plays a significant and almost certainly deleterious role in the process. Further, addition of excess acetaldehyde to adduct **3a** in d_8-THF led to rapid discoloration (dark red to pale orange) and complete consumption of adduct **3a** to give a complex mixture of unidentified products, implying that the acetaldehyde also plays a role in catalyst decomposition.

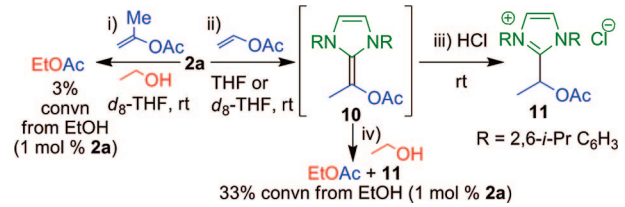
Lin et al. reported that the acetaldehyde produced in the vanadium(V)-mediated transesterification of vinyl acetate leads to reduced yields due to acetaldehyde-induced catalyst degradation.[20] The authors found that the use of isopropenyl acetate led to significantly improved yields. However, in our hands, addition of isopropenyl acetate to a solution of carbene **2a** in d_8-THF led to little or no consumption of either compound. This appears to indicate that the displacement of the acetone enolate from the vinyl ester is either slow or that the position of the equilibrium lies significantly to the left. When a catalytic amount (1 mol %) of IPr was added to a solution of isopropenyl acetate and EtOH in d_8-THF, conversion of EtOH to EtOAc was slow (3% in 18 h), implying that the former is the case. In contrast, in the presence of catalytic IPr (1 mol %), the reaction between vinyl acetate and EtOH proceeds to 33% conversion of EtOH to EtOAc in less than 30 min, at which time adduct **11** is the major imidazolium-derived species, leading us to believe that vinyl acetate reacts with IPr in a fashion similar to that for vinyl benzoate: addition of vinyl acetate to IPr in d_8-THF gives rise to the rapid formation of a new imidazolium-derived species characterized in situ as adduct **10**. Addition of HCl to a solution of **10** gave protonated adduct **11**.

(18) Compound **6** may also undergo *O*-acylation to give adduct **3** directly.

(19) Based on the proposed mechanism of benzil rearrangement in the presence of an NHC: Lachmann, B.; Steinmaus, H.; Wanzlick, H. W. *Tetrahedron* **1971**, *27*, 4085–4090.

(20) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 997–1000.

Scheme 4. IPr-Mediated Transesterification of Alkenyl Acetates



In conclusion, we have identified new and unexpected species formed in the IPr- and IMes-catalyzed transesterification of vinyl esters that imply that the reaction mechanism is significantly different from those proposed so far for this kind of process. It is not possible to distinguish between the two proposed mechanisms on the basis of our results, and investigations are ongoing. However, a literature report on the kinetic resolution of racemic secondary alcohols by a chiral NHC reveals different ee's when methyl acetate (0% ee) is used as the acylating agent in place of vinyl acetate (29% ee)[11,21] under similar conditions. Although not conclusive, this may imply that these reactions do not proceed via the same final bond-forming step, as would be the case if the acylating agent in both cases were an acyl-imidazolium species, which is consistent with the mechanism proposed in Scheme 3b. We believe that the information reported here will be helpful in order to develop a deeper understanding of the NHC-promoted transesterification of vinyl esters and should be seen as a consideration for the continued development of NHC catalysts for the kinetic resolution of racemic secondary alcohols.

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Supporting Information Available: Experimental details and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This may also be attributed to the MeOAc requiring a reaction temperature of −20 instead of −78 °C as required for vinyl acetate.